DR. ELLENBERG: That answers my question, but let me rephrase that for my benefit and, thinking aloud, the panel's benefit.

My sense of that response is that the ruling did not have to do with the issue of standard of care. It went back to the issue of having a heterogeneous control group. So let me follow on with that.

You in defining the entrance drug criteria or --

DR. COSGROVE: Can I respond to the question before I lose -- I'm trying to keep track of all the questions.

DR. ELLENBERG: I haven't asked the question yet.

(Laughter.)

DR. COSGROVE: Well, I know, but I think it's very, very important to point out that we as the investigators were very perplexed, very cognizant of these issues. I mean of the design study, of a single arm study. We did not propose this initially. We proposed a control arm, and we figured that the best

control arm, albeit less than perfect for a number of reasons which I'll go into, but we figured that the best control, the most suitable control would be a fibrin glue of some sort because similar in administration, really similar in terms of some of its properties, although it is a biologic device with all of the attendant risks that can occur from a biologic device.

In terms of indications for use, it would be very similar. In terms of actually adherence, we couldn't test it properly with a Valsalva because often when you do a Valsalva with fibrin glue, it just lifts off, and then you say, "Well, now I'm going to have to scrape it all off and put on a new one," and so you couldn't test it appropriately.

But we were willing to deal with some of those issues, and then we went to the FDA. We got their input, and were advised that using a control group, using a non-FDA approved device, we were not going to be allowed to do that.

So that was the binder. That was the handcuffs that we were placed into, and then we chose

the next best alternative, in our opinion.

DR. ELLENBERG: I'm afraid I don't see the handcuffs that you had, but let's pass on that. I think you've given your response to the question.

My second concern has to do in our interpreting the safety data and the efficacy data with a question as to your definition of endpoint being the watertight seal. Could you talk a bit about why the endpoint was not infection, for example?

I'm not asking if that would have been the specific endpoint, but why you did not choose an adverse event which you have listed very clearly in the past several minutes can take many forms; why that was not the endpoint rather than a watertight seal at some point close after surgery and then thereon, which seems to me in reading through the materials is more a surrogate endpoint than what you're really after, which is no complications.

Why did you choose the watertight seal at the endpoint?

DR. COSGROVE: Well, no neurosurgery is done without complications. So you know, there are so

many adverse events. If you're going to choose an adverse event as your endpoint, it's very difficult to make the connection that it was anything to do with your study.

So we chose the intraoperative endpoint of a watertight seal as something that could be easily defined. It's a binary observation, and as the essential aspect in wound healing if you are not getting a watertight seal at the time of surgery when you're actually closing the dura, it is the necessary achievement or objective in order to down the road reduce the complications associated with a non-watertight dural closure.

DR. VAN LOVEREN: If I might, I would also say that the application for this device is as a sealant to prevent CSF leak, not as a protection from infection. Although infection stands as a potential adverse outcome similar to other outcomes and highlighted itself, I don't think it's a legitimate endpoint. That's not what the application is for.

DR. ELLENBERG: No, I understand that.

DR. VAN LOVEREN: Okay.

DR. ELLENBERG: But if the outcome was different, the application would have been for something different, but I understand your point.

In the area of efficacy, again, on page 18 of your joint presentation -- I believe it was the top slide -- there's a list of the post surgical eligibility, such as the size of the hole left and then there's a whole other list. So that patients who are essentially excluded from the study post surgery if they did not meet these conditions.

DR. COSGROVE: Interoperably.

DR. ELLENBERG: Excuse me, yes. I misspoke.

In terms of those patients, did you make any attempt to see how those patients did? Did you catalogue the aspects of the reasons they -- which of your criteria they missed because my sense is that that could be quite informative in terms of both efficacy and safety? Is that data available?

DR. COSGROVE: Yes, it is. It is available, and I can get you a complete analysis of those cases. There were 23 cases that were excluded

on the basis of this interoperative criteria. Those are the patients you are talking about, and we have that data. We even have follow-up data because they were actually enrolled in the trial and we can get you that data in a little while.

DR. ELLENBERG: There are enrolled in the trial in the sense they followed the protocol?

DR. COSGROVE: Well, they were continued to follow throughout the trial. I mean, we do know what they -- no, I'm sorry. They weren't enrolled in the trial, but they were followed, and we have some of the data.

PARTICIPANT: I'm sorry, but we documented their --

MR. ANKERUD: Go to the microphone. State your name.

DR. COSGROVE: We know the reasons why they were excluded. Oh, okay. I'm sorry. But they were not followed to outcome. I thought we had that.

DR. ELLENBERG: Fine, okay. I think, Dr. van Loveren, if you can stay up, on the issues of safety in terms of how this was presented to various

IRBs at the cooperating clinical centers, do the protocols specify that the safety review, not the efficacy comparison, but the safety review for purposes of informing various TSMB components or the IRBs themselves; did the safety review in the protocol indicate to the IRBs that the safety evaluation would be a literature based review? Comparison, excuse me. A literature based comparison.

DR. VAN LOVEREN: I'm not sure if we communicated that specifically to each IRB about how the --

DR. ELLENBERG: Well, did the protocol have that as an analytic approach to evaluation of safety? Because that would have been submitted to the IRBs.

DR. VAN LOVEREN: Right. I don't believe so.

DR. ELLENBERG: Okay. In terms of your follow-up post three months, are these patients still being followed?

DR. VAN LOVEREN: Well, they're being followed clinically, but not for purposes of this

study.

DR. ELLENBERG: So you don't have control of their follow-up at this point?

DR. VAN LOVEREN: No.

DR. ELLENBERG: If the panel advised FDA that it would be useful for a long-term follow-up, would you have the capability of reinitiating the follow-up or are there informed consent issues? Are there other things that might impede the re-contacting of these patients?

DR. VAN LOVEREN: No, I don't think that would be any impediment to that whatsoever.

DR. ELLENBERG: Okay. Thank you.

CHAIRPERSON BECKER: I think that everybody on the panel has had a chance to ask at least one question. I want to see if Crissy Wells is still there, if she has a question.

(No response.)

CHAIRPERSON BECKER: Mr. Balo, any questions?

MR. BALO: No questions.

CHAIRPERSON BECKER: So --

DR. VAN LOVEREN: Could I belabor one point? This is a very dangerous move on my part, to go back to a question that apparently was answered and bring it back up, but it's on the infection as an endpoint.

I mean, I think infection is so determined by risk profile. It's so sensitive to risk profile. To set an OPC ahead of time you don't really have the ability to do that without knowing what your patient risk profile is.

If your ASA scores are all high, you should pick a number, an infection rate of ten percent. If your operation times are all going to be less than 60 minutes, you should pick a number that's in the two percent range.

DR. ELLENBERG: Certainly, but if you were in a controlled clinical trial situation, then that would be doable.

DR. VAN LOVEREN: Yes.

CHAIRPERSON BECKER: We'll have a chance for one or two more questions, and there's going to be an opportunity in the afternoon for even more

questions.

Dr. Germano.

DR. GERMANO: A question on safety. I don't see any data on seizures. Should the panel assume that the 111 patients did not have perioperative seizures?

Obviously when the compound touches the brain, there is a concern that seizures can be induced, whereas seizure studies done in the rats and dogs?

DR. CAMPBELL: Yes. The preclinical studies evaluated implantation into the rat. There was also hydrogel extracts that were injected into the cisterna magna and lateral ventricle. There was preclinical studies in the canine model I showed you.

DR. GERMANO: How did you monitor the seizures in those animals?

DR. CAMPBELL: They were clinically evaluated immediately after application and regularly daily by veterinarians. There were no signs of seizures or clinical abnormalities versus the control animals which were saline alone.

DR. GERMANO: Did you do any EEG studies?

DR. CAMPBELL: No.

DR. GERMANO: For the clinical component?

DR. COSGROVE: Seizures were reported in the adverse event summary sheet. I'm just looking through the adverse events.

DR. GERMANO: It's not there.

DR. COSGROVE: It's not there. There were three seizures reported in the final report.

CHAIRPERSON BECKER: Dr. Jayam-Trouth.

DR. JAYAM-TROUTH: A couple more points. One is the cognitive problems that you say that you had in page 27 of your patients and the speech difficulties in ten your patients, five of your patients with cognitive problems, 34 of your patients with premium nerve deficits. I mean these were all relevant to the DuraSeal itself?

DR. COSGROVE: That's correct. I mean, this speaks to the patient population and the procedures performed on them, and none of these were unexpected, and upon review by the CDC, none of these were deemed relevant to the DuraSeal application.

These, you're talking about aneurysmal surgery, cranial base surgery, microvascular decompressions, tumor surgery, all of these things, and you know, these are a standard array of neurologic deficits that when you're actually recording each and every adverse event, whether it's related or not to the DuraSeal, these are sick patients and you just have to be a neurosurgeon to understand that and a neurologist, I guess, you know.

(Laughter.)

DR. COSGROVE: Of course, you may find more things than we find I'm sure.

DR. JAYAM-TROUTH: In all of your QRAs that you did --

DR. COSGROVE: Yes.

DR. JAYAM-TROUTH: -- you know, did you actually show that there was a pressure change, the CSF was being held up, you know, and that the surgery would be helpful in these patients?

DR. COSGROVE: You know, that was a clinical decision for surgical intervention on the QRA patients was made by the site investigator, and there

was nothing in the protocol looking for CSF flow studies or anything like that. You know, typically they have to have the appropriate clinical symptomatology in that the tonsils typically have to be down to the level of C1, you know, before we would consider doing a decompression, but as you well know, the clinical symptomatology from a QRA malformation can be quite diffuse, and so that's a clinical decision that the site investigator took care of.

DR. JAYAM-TROUTH: Okay. Dr. Cosgrove, for the record, there is no data on seizures in your presentation today. There is no data on seizures in the presentation that you submitted to the FDA; is that correct?

DR. COSGROVE: They're on the slides. I guess it was omitted in terms of the three patients who had seizures, but I believe it is in the -- yeah, I think we just have to look a little more closely.

CHAIRPERSON BECKER: Okay. Just a reminder that we will have a chance to ask questions this afternoon of the sponsor.

I think at this point we'll take about a

five minute break while the FDA gets ready to give their presentation, and we'll reconvene at 11 o'clock.

(Whereupon, the foregoing matter went off the record at 10:55 a.m. and went back on the record at 11:05 a.m.)

CHAIRPERSON BECKER: Okay. It's now 11:05, and I'd like to call the meeting back to order.

I'd like to give a couple of reminders. Firstly, when you speak, make sure you speak directly into the microphone so that the transcriptionist can actually get a transcription made.

And I'd like to remind the public that while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

We'll now have the FDA presentations on this PMA, and the first presenter is Dr. Peter Hudson. He'll be followed by Dr. Michael Schlosser. So Dr. Hudson.

DR. HUDSON: Great. Thank you.

Good morning. I'm Peter Hudson. I'm the lead FDA reviewer for Confluent Surgical's PMA

application.

The FDA review team consisted of myself. I did the lead review and the preclinical review. Dr. Schlosser, who did the clinical review. Ms. Silverman, who did the statistical review, she was unable to be with us today, and Dr. Telber Irony (phonetic) is here, another FDA statistician to help us with any statistical issues that might arise. Mr. Rangel, who looked up manufacturing information, and Ms. Braxton, who was a lead BIMO reviewer and looked clinical data integrity.

My presentation, I'm going to briefly go over the device description, look at the toxicology information, biocompatibility evaluations, and then go over the preclinical animal evaluations that were done.

The DuraSeal Dural Sealant System consists of components for preparation of an absorbable polyethylene glycol hydrogel sealant and a delivery system, the applicator and spray tips, and it's packaged in a single use kit.

The sealant is composed of two solutions

of polyethylene glycol ester and a trilysine amine solution referred to as the blue and clear precursor solutions.

When the solutions are mixed within the delivery system, it provides for a rapid in situ polymerization of the hydrogel that's intended to assist in the dealing of the dura mater incision line. The mixing of the components occurs right at the tip of the applicator just as the fluid exists the applicator.

The sponsor has done preclinical evaluations to characterize the product. The gel time is less than 3.5 seconds. The pot life, or the amount of time that the precursor solutions can be used after reconstitution is one hour.

They've done in vivo animal evaluations, as well as in vitro analyses, to look at the degradation rate to get an idea of how quickly the material might resorb, and they've determined how much the material will swell once polymerized. The gel will swell less than 200 percent. Two hundred percent volumetric swelling is defined as the percent weight

gain over a 24-hour period in a PPS bath would result, for a two millimeter thick layer of gel, would result in less than a one millimeter increase if the gel isotropically swelled.

The DuraSeal device consists of the following chemical components. I'm going to specifically discuss the PEG ester, the trilysine solution, the FD&C blue eye, and butylated hydroxytoluene.

Polyethylene glycol, or PEG, is approved by the FDA as a food additive and is used in topical and oral drug formulations. It's used in ointments and lotions, tablet binders, coatings for pills, suppository bases, and in veterinary drugs.

In addition, PEG has been approved by the FDA as a surgical sealant. FocalSeal by Genzyme and CoSeal by Cohension Technologies are both PEG based surgical sealants. The FocalSeal product is used in lung indications and the CoSeal product is used as a vascular sealant to assist in hemostasis.

The FocalSeal product consists of a PEG polymer of 31,500 daltons average molecular weight.

In comparison, the DuraSeal product is 20,000 daltons average molecular weight.

The half-life of PEG polymers increases with an increase in molecular weight. So a general inference from that would be that the DuraSeal product, its half-life could be anticipated to be shorter than the FocalSeal product.

To address PEG clearance, the sponsor did a number of blood chemistry evaluations specifically to address concerns about nephrotoxicity due to PEG clearance. They looked at BUN and creatinine levels. They looked at preoperatively discharge and at three months there were no abnormal blood chemistries noted.

Trilysine is the synthesis product of L-lysine. L-lysine is a naturally occurring amino acid. An extensive search of the toxicological databases did not reveal any associated toxicities with trilysine.

Butylated hydroxytoluene or BHT is an antioxidant and has been designated as GRAS, or generally recognized as safe, for use in food since 1959. It, too, a source of toxicology databases did

not reveal any significant associated toxicities.

The WNO, World Health Organization, or WHO recommendation for an acceptable daily intake of BHT is 125 micrograms per kilogram per day. The amount of BHT that patients would be exposed to in one application of the device is 1.3 micrograms per kilogram.

The no effect level that's been observed in mice and rats was 5,000 parts per million and 1,000 parts per million respectively for the mice and rats.

D&C blue #1 is a water soluble dye that's been approved by FDA for use in food, drugs, and cosmetic products. Lifetime exposure animal studies support an acceptable daily intake of 12 milligrams per kilogram per day. The amount that patients will be exposed to with one application of the device is approximately 1,000-fold lower than that.

The FDA has also determined that FD&C blue #1 is not is not carcinogenic is rodents after a lifetime exposure. However, the sponsor needs to submit a color additive petition, or a CAP, to the center for use of the dye in a medical device. They

need to submit a CAP to the Center for Food Safety and Nutrition.

The sponsor is currently involved in that process. This is a regulatory process that the panel doesn't need to consider in their deliberations over the safety and efficacy of the device for its intended use.

The sponsor has conducted standard biocompatibility evaluations of the device in accordance with guidance recommendations. The samples of the device were prepared in a way to be analogous to how patients would be exposed to the product in that the sealant plus any extractable chemicals and unpolymerized polymer would be included in the sample. The device passed all of these biocompatibility evaluations.

In addition, the sponsor looked at the immutogenicity of the product in four standard genotoxicity evaluations. The product passed all four of these.

No carcinogenicity testing was conducted in light of these findings and also in light of the

absence of any inflammation, suggesting that the individual chemical components would be considered to be transforming agents.

The sponsor has conducted preclinical evaluations to investigate the device's performance characteristics with respect to safety and efficacy. They've evaluated in vivo animal studies to look at the neurotoxicity of the product in a couple of different types of assays and also done in vivo evaluations for the persistence of the product to get an idea of its degradation and resorption characteristics.

Finally, they've also done reproductive toxicity, teratology experiments to look at that issue as well. I'm going to go over each of these evaluations.

In the canine cranial sealing study, the sponsor created a two centimeter long dural matter incision. They loosely repaired that with microsutures and then applied the hydrogel sealant or for the control dogs did not apply anything over the two millimeter gap in the dura matter.

Eleven of 11 control dogs showed CSF leakage at pressures less than 20 centimeters of water, whereas only one of 12 animals showed CSF leakage.

Marked peridural adhesions were observed in three of three controlled dogs at seven days and in one of three controlled dogs at 56 days, whereas with the DuraSeal treated animals no adhesions were observed.

Valsalva maneuvers conducted at one, four, seven, and 56 days showed CSF leakage at lower pressures in the controls than in the treated animals. Histopathology of the control also showed thick dural fibroplasias and minimal injury to the underlying brain tissue, whereas in the DuraSeal treated animals no fibroplasia was observed and, gain, limited injury to the underlying brain tissue was seen.

Implant residual material was apparent at seven days, but was not detected at 56 days out. So the results of this experiment demonstrated that the product could effectively seal a dura matter incision line; that there wasn't fibroblastic or adhesion

formation observed with the device in the healing process, and that the implant material was gone within a two-month period.

In the rat brain parenchymal implant study, the sponsor investigated the local irritant and neurotoxicity of the device, as well as they looked at systemic toxicity of the product as well. They implanted one by one by one millimeter sections of polymerized DuraSeal and/or used absorbable gelatin sponge and fibrin sealant as control implants. Absorbable gelatin sponge and fibrin sealant obviously are materials that are used in closure of the dura matter.

Under microscopic evaluation, there was no evidence of a local irritancy effect or neurotoxic effect detailed examinations, the clinical science of abnormal or diseased tissue, and neurologic assessments were conducted at four, 15, 28 and 42 days. The DuraSeal product was considered to be inert, space occupying mass that did not elicit an irritant effect and did not elicit a neurotoxic effect.

In this neurotoxicity evaluation, the investigators looked for neurotoxicity due to injection of the material into the brain. Extracts from the polymerized sealant were prepared and then injected either into the lateral ventricle or cisterna magna and compared to control buffer.

There was no evidence of treatment related neurotoxicity in the DuraSeal or control animals for a 14-day take-down examination, and the only alterations seen were due to trauma induced by the cannulation of the tissue, and there was no macroscopic or you could not see any encapsulation of the material that was injected.

The sponsor also conducted an in vivo model to characterize the degradation and resorption characteristics of the material. They implanted various formulations of DuraSeal into the subcutaneous sites in rats. The various formulations were -- well, they looked every two weeks out to 14 weeks. They excised the implant sites and looked to see if the material was still there microscopically, and they found that the material was degraded with an eight-

week period or of shorter duration.

And these results correlate well with what was seen in the canine cranial study. The material was gone within 56 days.

For comparison, clinical CT imaging showed a reduction of approximately 75 percent of the extradural space where the material had been applied at three months.

Finally, the material was investigated for any potential developmental toxicity or any kind of teratogenic effect. The product was injected in a single subcutaneous administration in rats. The DuraSeal did not cause any developmental toxicities on any of the parameters measured in the dams or the fetuses.

So in conclusion from the preclinical information, the device's chemical components don't raise concerns toxicologically, either the individual components themselves or the amounts of those components that patients would be exposed to.

The device, the sponsor has done standard biocompatibility evaluations of the product, and it

has been demonstrated to be biocompatible. The tests that they've conducted are those that are recommended for medical devices having this type of tissue contact and for this length of duration.

The animal model evaluations approximated the use in humans and showed that the device could work as intended and did not elicit any tissue toxicities, and there's no evidence to suggest that the device can cause carcinogenesis or reproductive toxicities.

This concludes my portion of the presentation of the update presentation, and Dr. Mike Schlosser will give you the clinical information.

DR. SCHLOSSER: Good morning. I'm Dr. Michael Schlosser. I'm a neurosurgeon and medical officer for Division of General Restorative and Neurologic Devices, and I'm going to go over my clinical review of the DuraSeal study.

To start, the study was done under IDE. The objective was to evaluate the safety and effectiveness of the DuraSeal Dural Sealant System as adjunct to a sutured dural repair during cranial

surgery to provide a watertight closure.

As we've heard, the design was a prospective, multi-center, nonrandomized, single arm clinical study with a three-month follow-up period.

This is the proposed indication for use statement for the device. The DuraSeal Dural Sealant System is intended for use as an adjunct to sutured dural repair during cranial surgery to provide watertight closure.

I just put that up there because one of the panel questions, Question 3, surrounds the appropriateness of the indications for use, and some of the discussion we've had this morning already kind of touches on some of our concerns about the appropriateness of the patient study and supported this particular indication for use.

I'm going to talk a little bit about the clinical trial design. We heard a lot about this already this morning, but a few important points I want to touch on, particularly some of the inclusion and exclusion criteria.

As we heard, there were two sets of

inclusion and exclusion criteria, those applied pre-operatively to screen patients for enrollment and then those applied interoperatively to determine which patients would be treated. So to start with I'll talk about the preoperative inclusion criteria. As we heard, these are all elective cranial surgeries that had dural incisions. So no nonelective cases were allowed.

Adults between 18 and 75.

The surgical wound classification is expected to be clean or Class I. That's why the CDC definition. And a little bit later I'm going to talk or go through exactly what that CDC definition is, as it becomes important.

And then finally, informed consent had to be signed.

Exclusion criteria, there were some important ones that I've selected. Translabyrinthine, transsphenoidal, and transoral approaches were eliminated. This also falls in line with the CDC Class I for a clean wound, and exposures to these bases would make a clean contaminated wound.

Penetration of other air sinuses or mastoid air cells. In addition to this being a potential source of infection, these are also other routes that CSF obviously can use to escape and cause a CSF leak.

Prior procedure in the same location. So these were all first time surgeries at that location.

Prior radiation or any planned radiation to the site in the exclusion criteria.

Any evidence of systemic or local infection.

And then chronic steroid use that had not been discontinued at least six weeks prior to the trial were all reasons for exclusion.

The interoperative inclusion criteria, and these were the patients who were successfully screened, were taken to the OR as part of the study. They were then examined again interoperatively to determine if they still met the criteria. So the surgical wound had to end up being clean or Class I so that if there was an inadvertent exposure to an air sinus or another reason why the wound would no longer

be classified that way, the patient would be eliminated.

Durotomy had to be at least two centimeters in length, and then CSF leak had to be present, either a spontaneous leak or after Valsalva.

I'm going to come back to that part about the spontaneous and Valsalva leaks in a couple of slides.

And finally, the interoperative exclusion criteria, the use of synthetic or nonautologous duraplasty materials. So these are all new patients who could achieve or in which the surgeon could achieve an appropriate closure using either primary closure techniques or using only autologous grafts.

A gap of greater than two milliliters, as we've heard about in a little bit of detail this morning, was a reason for exclusion, and then finally any incidental finding of the preoperative exclusion criteria.

So I'll just pause here to mention that these points I've brought up describe kind of how the population was taken from just everyone presenting for

a craniotomy down to the patients who were included in the trial, and it's important for the panel members as they kind of already have started talking about to take that into account when we starting thinking about who are the patients that are studied and who are the patients that the device should be used in.

And that, again, relates to our Question 3 in the panel questions.

Moving on in the clinical trial design, the primary efficacy endpoint, as we heard, was no CSF leakage after up to two dura sealant applications. So the patients were challenged with the Valsalva maneuver. If the DuraSeal was applied, they were challenged again. If they leaked after that first challenge, they could then have an additional application, and then after that second application, any patients that continue to leak would be considered a failure.

The study success criteria was set at 80 percent. This was based on experience and pilot data submitted as part of the IDE. The plan was to use descriptive statistics of the success rate of the

study and then compare it to that study success criteria.

And then in terms of safety, all adverse events as we noted were reported to FDA. We had a specific interest in CSF leak and infection for obvious reasons.

The plan during the IDE phase was to do descriptive statistics on the safety events. There was not actually a plan during the IDE phase to use a literature or other control group. The comparisons to the literature were things done during the evaluation of the PMA data after it was submitted.

Specifically, CSF leak was an important concern as a safety endpoint, and so a specific definition of CSF leak was included. We went through this. The sponsor went through this already this morning, but just to reiterate, any CSF leak or pseudomeningoceles that required a surgical intervention, which was breaking of the skin, any CSF leak confirm by diagnostic testing, and then finally any leak confirmed by clinical evaluation.

So this basically breaks down to all leaks

of fluid that could be determined to be CSF, and then in addition to that, all pseudomeningoceles that required some kind of intervention. So the only thing being excluded are pseudomeningoceles that didn't require an intervention that involved breaking the skin.

I'd like to speak for a moment now about the design rationale for the study. There are several points to make here.

The first is the fact that the goal of the device was to obtain a watertight closure meant that the device lent itself to a study that used an interoperative criteria. Since that could be easily evaluated and kind of visualized interoperatively, the use of a study success criteria with a specific goal and then a single treatment group to compare to that success criteria seemed like a good match.

In addition, as we've now heard a lot about this morning, there are no approved devices for this indication. Despite that, there are many devices that are very commonly used in our surgical practice as an adjunct to sutured dural closure, such as fibrin

glues or other synthetic blues that are altogether being used off label for that purpose.

Since there is no approved device with known safety and effectiveness, no single device that could be used as a control, the idea of using a heterogeneous control group which is standard of care was raised during the IDE stage and the pre-IDE stage of this device.

However, a study that would randomize patients to standard of care would be allowed by the FDA regulations, would put us in the position of having to assess a device safety and effectiveness as compared to a heterogeneous group of other devices the safety and effectiveness of which are not known.

So in a sense you have to evaluate a study whereby your control group or your benchmark is devices with unknown safety and effectiveness, and so we felt that there was significant weaknesses in that study design as well.

Just a note about valid scientific evidence. A PMA application must demonstrate safety and effectiveness through valid scientific evidence.

This is per the Code of Federal Regulations 860.7, the definition of valid scientific evidence, which includes well controlled investigations, partially controlled studies, studies in objective trials without matched controls, well documented case histories conducted by qualified experts, and finally, reports of significant human experience with a marketed device.

During the pre-IDE and IDE stage the sponsor and FDA work together to determine an appropriate study design that fits within this definition of valid scientific evidence, addresses the important safety and effectiveness issues for that device and also satisfies the least burdensome criteria of the 1997 Medical Device Modernization Act. And this process was also undertaken with this particular device.

Now, moving into the study results, the population, there was 303 patients screened to enroll 132. Of those 132 patients enrolled, 111 of those patients were treated with the DuraSeal sealant.

Here the patients who were excluded out of

the 132 to get to 111, there are six patients due to a sinus penetration; seven due to a gap greater than two millimeters; three dues to less than three millimeter gap from dural incision to bony edge; and six due to the use of a nonautologous duraplasty material.

It is important at this point for me to notice that there are no patients who were excluded because they didn't leak. So all the patients who were considered for inclusion in the study either leaked spontaneously or leaked with a Valsalva maneuver.

So the idea behind using the presence of an interoperative leak was to select for a population that had leaking CSF and, therefore, were at higher risk for the morbidities and mortality associated with postoperative CSF leaks.

However, in this study, all of the patients leak. So there really was no selection based on any kind of predilection towards future CSF leak, which means that the study really describes more of an all comers approach for craniotomies than a specific subpopulation at risk for leaks.

The follow-up, as we've seen in the sponsor's study, there were two patients that died before the three-month follow-up period, and there were two patients who refused to participate at the three-month assessment, giving a total of 107 patients available at 90 days.

However, since we were using an intra-operative criteria for the efficacy endpoint, 100 percent of the patients were available for that endpoint.

This is just a chart showing the different types of cases that were included in the study, and as you can see, it kind of runs the gamut of typical intracranial neurosurgical procedures, including vascular procedures, nerve decompressions, epilepsy, and a variety of different tumors.

The primary efficacy endpoint. All patients leaked intra-operatively, as I've already mentioned with the Valsalva or spontaneous leak. This is the breakdown. Sixty percent had spontaneous leaks, and then the final 40 percent had a leak after Valsalva. I'll mention there that that also plays

into our Question 3 to the panel when we ask whether or not the difference between someone spontaneously leaking and someone who leaks after Valsalva is important in determining how the product should be used in the future.

One hundred and five out of 111 subjects had no CSF leak after the first DuraSeal application. So they had the sealant of Valsalva was then done to 20 centimeters. One hundred and five of those patients didn't leak.

The remaining six had a second application, and no patients leaked after their second application. However, there were two patients who only had a Valsalva to ten centimeters of water rather than the required 20, and so if we take the conservative approach, assuming those two patients would have been failures had they had the 20 centimeter Valsalva, then we get 109 out of 111 for the success rate, which comes to 98.2 percent.

Looking at this statistically, this is the study success, at 98.2 percent the success criteria set out during the IDE phase of 80 percent. The

brackets here represent the 95 percent confidence interval, and as you can see, the lower bound of the confidence interval which is at about 93 percent is still well above the 80 percent study success criteria set out at the beginning of the study.

So now I'll move on to talk in a little bit more detail about safety. This is a summary of kind of the important serious adverse events seen in the sponsor's data. The items selected in yellow are the items that I've chosen to look at in a little more detail.

The deep wound infection, there were nine such events in eight patients. As the sponsor mentioned, they didn't cascade events. So there was one patient who presented on two separate occasions with a wound infection that was counted as two separate events even though it appears from the clinical history that the patients simply had an ongoing infection over the course of the follow-up. But that was counted as two separate events, giving nine events in eight patients.

CSF leaks, six events, and then bacterial

meningitis, two events in two patients. Again, there's overlap here in that one patient had both a deep wound infection and associated meningitis. So that patient had two events recorded even though it was probably one infection.

The other events listed here are stroke, hydrocephalus, aseptic meningitis, cognitive disturbance, cranial nerve deficits, are typical events you'd seen in a post craniotomy population and not of a significantly high magnitude to raise a concern.

I'll start by examining postoperative CSF leak in a little more detail. This was looked at as both a safety/adverse event endpoint as it was collected, but we also examined CSF leak to determine if any additional information about the benefit of the device to these patients could be gleaned from the CSF leak results.

Post-op CSF leaks, as I mentioned, occurred in six cases. There were three pseudomeningoceles which required some kind of surgical intervention, thus fitting the criteria.

There were two overt CSF leaks through the incision, two out of 111, giving a rate of overt incisional CSF leaks, and there was one leak discovered intraoperatively which we've heard some detail about that case from Dr. Cosgrove. This is a patient who underwent a debridement of a wound infection, removal of the DuraSeal, at which point in time there seemed to be some pooling of CSF, and a lumbar drain was put in to prevent future leak of that CSF through the wound, but since the patient underwent a surgical procedure, being the lumbar drain, it was felt they met the criteria for CSF leak set down in the study and, therefore, were counted, giving us an overall leak rate of six out of 111, or 5.4 percent.

So as I mentioned, the plan in the study was to do descriptive statistics, which was done giving us that 5.4 percent rate. However, to understand what that rate means a little better, FDA undertook a comparison to the literature.

And so I've selected out a few studies from that large literature review that was done that I think are interesting to point out. The first is the

BioGlue study, which was done by Kumar, et al. This was a study done outside the United States on the synthetic glue that was used as an adjunctive dural sealant, but who was not approved in the United States for that use.

Two hundred sixteen elective craniotomies were included. There was only a six-week follow-up period required. CSF leaks were screened for by physical exam only, and only overt CSF fistula is reported. In the literature article there was no mention of pseudomeningoceles, and so there were two cases, or 1.2 percent, of overt CSF fistulae, but as it's obvious from this slide, their definition of CSF leak was different from the one used by the sponsor. So it's difficult to compare apples and apples with this study, but if we look at the rate of overt CSF fistula in the DuraSeal study, which was 1.8 percent, it's similar to the 1.2 percent seen here. However, we don't know anything about the other types of leak in this BioGlue study.

Another study on DuraPatch, which is a dural substitute, involved -- and this was published

by Von Wild in Surgical Neurology in '99. One hundred and one elected craniotomies, so again, only elective cases just like the DuraSeal study. They excluded lesions of the skull based on invasion of the frontal sinus, and all of these cases were such that an allograft to patch the dura was needed.

So the exact details of the types of procedures is not robust since this is just a literature article. You can make the assumption that these are more complicated dural problems, larger dural holes that could only be fixed with an allograft patch.

You can certainly make the assumption that none of these cases could be closed simply primarily with stitches. So a slightly different population in terms of the problems facing the surgeons in getting the dura closed.

Follow-up in this case was six months and did include CT and MRI. However, only 75 percent of the patients were available for that six-month follow-up and the only other follow-up was actually seven days or at discharge, and so most of the information

they have is on that seven-day follow-up, and then they have a substantial 25 percent loss when they go out to their six months.

CSF leaks were clinically diagnosed. Again, a very specific definition like was used in the DuraSeal study is not provided. However, they had a much higher rate of 12.9 percent, a numerically higher rate.

All of those patients had some kind of CSF leak that would have been included in the DuraSeal study, but given that we don't have all of the details on how they selected the CSF leaks, it's tough to know if the number had they used the same rigorous criteria we used would have actually been higher or lower. But just for comparison's sake, we see a higher rate here of 12.9 percent.

And then the last study I'll mention is a study of aerosolized fibrin sealant. So as we've mentioned now, fibrin glue is very commonly used in these neurosurgical procedures as an adjunct. This study looked at using an aerosolized delivery system versus the standard fibrin sealant delivery through a

syringe. It was a retrospective study, 295 cases with the aerosolized variety and 214 with the normal application. It was only elective supratentorial craniotomies. So that's a subset of the population that was seen in the DuraSeal study, which also included infratentorial craniotomies, and they excluded skull based approaches.

There was only a two-week follow-up minimum required, and again, a specific definition of CSF leak was not given. For the aerosolized group the leak rate reported is 3.1 percent, and 8.9 percent for the non-aerosolized group.

And, again, all nine leaks that were reported in the aerosolized group were described in the paper as either being treated with subcutaneous punctures or with lumbar drains, meaning that they did fit into the criteria for the DuraSeal study. However, since we don't have a specific definition given to us in the paper, we're not sure how exactly they were selecting for those leaks.

So this is summarized. It goes without saying that there are numerous reports in the

literature of CSF leaks across a variety of different types of surgical procedures, and reporting a variety of different results, but I felt these three articles kind of gave us a span of what's available.

The rate of the DuraSeal study, 5.4 percent. The BioGlue study, which obviously had a rigid definition of only CSF fistula, had a lower number. The DuraPatch study, which didn't give us a definition, had a higher rate of 12.9 percent, but again, this is probably a different problem facing the surgeon in terms of achieving a dural repair than the one that was studied in this study. And then the aerosolized fibrin sealant which was a larger study and probably a more heterogeneous group of craniotomy patients, but was retrospective and, therefore, is subject to some of the biases associated with the retrospective design. It kind of shows some rates that kind of span the DuraSeal rate, 3.1 percent and 8.9 percent.

So we have seen that the rates seen in the DuraSeal study certainly fall within the range reported in the literature, and depending on how they

selected their CSF fistulae, the numbers came out either higher or lower, but certainly the 5.4 percent fell within the range.

Moving on to infection, there were nine wound infections, as I mentioned, eight deep infections and one superficial. All of the deep wound infections required a reoperation, one being debridement and the other seven debridement and bone flap removal.

The one superficial infection was treated with antibiotics. The overall wound infection rate, therefore, is 8.1 percent. The 95 percent confidence interval on that rate is actually quite wide, going from 3.8 to 14.8 percent.

There were additionally two cases of meningitis. As I mentioned, one of those cases was in a patient who also had a wound infection, and so if we look at a number of patients who had a procedure related or neurosurgery related infection, it would be ten out of 111 or nine percent.

I mentioned I would come back to the CDC definition of wound classification, and here it is.

Clean or Class I wound is an uninfected surgical wound in which no inflammation is encountered, and the uninfected respiratory alimentary, genital, and urinary tract is not entered.

In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Surgical incision wounds that occur after nonpenetrating or blunt trauma can be included in this category, which obviously means penetrating trauma would not be.

And then clean-contaminated or Class II includes penetration of the air sinuses, the alimentary, genital, or urinary tracts, if done under a controlled situation, and also includes cases in which there's unusual contamination, meaning some kind of breach in sterile technique in the OR resulting in a contamination, but no obvious infection. So breach of the air sinuses in the presence of an infection would then bump it up into the next level which would be a contaminated case.

So this is the definition by which the patients for the study were selected. The literature,

however, doesn't really make use of the CDC definition just by itself because studies have identified other factors which are important for predicting infection.

We've heard about some of those from the sponsor's presentation. They include the length of procedure being greater than two hours, implant of foreign body, particularly shunts, which neurosurgeons in the room are well aware of, and then ASA score.

There actually are other risk factors as well, but I'll focus on these.

We've heard already about the Narotam study. This was the 2,294 patients in which he sought to determine what the risk factors for infection were in neurosurgical cases. He used slightly different criteria. He defined clean as elective surgery, not containing one of the above risk factors, and those risk factors are entry into paranasal sinuses, cranial base fractures, breaches in standard surgical technique, and surgery greater than two hours.

So it becomes quickly apparent that there are some things in here that weren't included in the CDC definition. There are also things in here that

were not included in the Class II clean-contaminated CDC definition. So this kind of lies somewhere in the middle and doesn't really fit into one definition or the other very well.

And then contaminated in this study were open fractures, contamination of the site known to have occurred, CSF leakage, and repeat surgeries.

So if you break this down now and look just at the clean contaminated cases in this study, he then subdivides even further. So we're looking at the subgroup of clean contaminated and then subgroups of that subgroup being just the patient in which entry into the sinuses occurred, fractures of the cranial base, surgery at two to four hours, and surgery at greater than four hours.

And then down here at the bottom I have the infection rate for the truly clean cases. So patients who had none of those, and that rate is extremely low, 0.8 percent.

So in comparison to all of these rates, the clean-contaminated class as a whole had a statistically higher rate than the clean case.

However, an important point to note here is that this surgery two to four hours was 5.6 percent. Surgery greater than four hours was 13.4 percent.

However, that difference was not statistically significant in his study, and so these numbers look different, but in actuality all he could say was that surgery greater than two hours was a risk factor. Greater than four hours didn't prove to be statistically worse than the two to four-hour group.

It's also kind of an important point of the power of these studies. I mean, you have 178 patients here and 23 here, which was not enough to be able to tell the difference between these two rates from a statistical standpoint.

The DuraGen study, which was actually published by the same author, was a study looking at dural closure using the DuraGen product, which is a collagen product, or a control group in which it was not used, and we can see here these stratified by clean, clean with foreign body, clean contaminated in all of the cases.

As was mentioned by the sponsor, foreign

body use was not rigorously collected on case report forms for this study, which is why I just haven't included anything under that column.

However, we do know about clean versus clean-contaminated for the DuraSeal study. There were no infections in the seven clean cases, and there were 12 infections out of the 102 clean-contaminated, giving us a rate of 11 percent, which is similar to the 12 percent seen in the treatment group of the DuraGen study.

The control group had a smaller rate of 4.3 percent, but again, this difference was not statistically significant in the DuraGen study, which, again, just kind of reminds us of the power of these studies given how many cases, 91 in '74 in clean-contaminated.

Looking at just the overall totals, we have the 10.8 percent in the DuraSeal study compared to five percent and 4.4 percent in the two groups of the DuraGen study. As the sponsor mentioned, this number here, 12, is higher than the ten that I presented on a previous slide because Narotam used a

little more strict definition, including patients with red wounds as counting as wound infections. That wasn't part of the ID study design, and so they weren't counted kind of initially, but were just included for this comparison.

A couple of other studies. These are a little bit older studies that looked at the use of antibiotic prophylaxis. There are, however, larger studies and prospective randomized controlled studies.

The first one by Young, published in '97, looked at 846 clean procedures. Two hundred and fifty of them were major craniotomies, and they had one-year follow-up. And they defined clean cases as intact skin without evidence of infection. So again, a different definition, though it seems to be quite a liberal one in that they did not necessarily specify their sinus penetration. They didn't talk about including trauma, blunt trauma versus not including it. They just kind of had this more broad definition.

Their infection rate with antibiotic prophylaxis for the whole 846 was .9 percent. If you look just in the craniotomy, the infection rate was

zero percent.

Length of procedure was not reported. ASA score was not reported. So there are a few risk factors to infection that we don't know about for this study.

Another very similar study by Bullock was another prospective randomized study of antibiotic prophylaxis. This included 416 clean craniotomies. This study did exclude breaches of air cells in a similar fashion to what was done in the DuraSeal study, and they did report OR time, with a mean OR time of 107 minutes and a standard deviation of 64 minutes. So the average being less than two hours, though with a wide standard deviation, meaning that there were subpatients greater than two hours.

Infection rate in this case was 2.1 percent without antibiotics versus 5.8 percent with antibiotics. So it seems like slightly higher than the previous study, but in terms of the confidence intervals and statistical differences, probably just very similar numbers.

We've heard a little bit about the

DuraSeal pilot study. This was done in Europe. It was not an IDE study. There were 47 patients. In that group there were two wound infections, 4.3 percent. However, again, a wide confidence interval of .52 to 14.5 percent.

There was one stitch abscess, which doesn't meet the CDC criteria for a wound infection. So it wasn't counted appropriately.

And all but one case in the study were greater than two hours. So similar to the pivotal study, these were long, complicated cases, 38 percent greater than four hours, but the ASA scores were less. Only four cases that were greater than two, compared to 33 percent of the cases in the pivotal study that were greater than two.

So we have just as long procedures, but slightly healthier patients, and we get a similar number.

This table summarizes the studies that I've presented, and again, just like CSF leak, there are numerous studies in the literature that you can look at to try to estimate what infection rates are

for a craniotomy. I've only selected a few that I think are descriptive. I'll move on to the next slide because it shows the same data in a graphical presentation.

On the left here we have the studies that involve only clean cases. This, again, as I mentioned, the definition of clean can change from studies from one site to the next, but these were these prospective randomized studies of clean cases.

In the center are the clean contaminated cases and in the end, the DuraSeal studies which have a combination, though they did have a majority of clean-contaminated cases.

And the important thing to look at here really are the error bars, and so I think what you can see is that the error bars on both the DuraSeal study and also on this DuraGen study really kind of span the results seen in the other studies, and so it's difficult to make a statistical comparison or to say that this is either significantly higher than this or the same as this. I think those statistical comparisons are challenging, not only given all of the

differences in the study design, but just given the results.

If we even just forget about the fact that these are all different studies with different criteria and just look at their results, the error bars are wide. So really the results are kind of all falling within a very similar region.

I'm just going to come back to this difference between the spontaneous leakers versus the induced leakers with Valsalva. One of our panel questions refers to those two populations. So I broke the results down by those two groups.

The wound infection rate, 7.4 percent in spontaneous leakers, 9.1 percent in induced leakers. So really not very different.

And CSF leak, the same kind of result, 5.9 percent in the spontaneous leakers versus 4.5 percent in the induced leakers, but those numbers are close and not statistically different from each other.

In conclusion, the sponsor reached their primary efficacy endpoint as set out in the study design of a success criteria greater than 80 percent

with their 98.2 percent, the lower bound of the 95 percent confidence interval being 93, and greater than 80 percent criteria.

Postoperative CSF leak rate was 5.4 percent. The wound infection rate, 8.2 percent, and the procedure related infection rate, nine percent.

I put those numbers up there by themselves because I think after the intellectual experience of examining the literature and trying to come up with a good comparison, we really come up with the conclusion that the results in the literature are varied. They use different definitions. They use different criteria. They're not IDE studies. There's a number of reasons why we can't come up with one good number as the comparison, and so I would say that the best we can learn from these studies is that with the use of the device, this is the CSF leak rate and this is the wound infection rate.

Thank you.

CHAIRPERSON BECKER: Thank you, Drs. Hudson and Schlosser.

Does anybody in the panel have a question

for the FDA?

DR. CANADY: I just have one question. It is really the same question.

What was the control group in the DuraGen? What kind of defects were left?

DR. SCHLOSSER: It was patients in which the dural closure could not be completed with sutures alone, and so they didn't specify any specific number, like two millimeters that was used. It was simply patients in which an augment to the dural closure was required, and so it's a heterogeneous group in terms of the size the hole was.

CHAIRPERSON BECKER: Dr. Haines.

DR. HAINES: For Dr. Hudson, I just wonder if there's any toxicity data on direct application of blue dye in the spinal fluid.

DR. HUDSON: Of the blue dye?

DR. HAINES: Yes.

DR. HUDSON: No.

CHAIRPERSON BECKER: Dr. Jensen.

DR. JENSEN: Dr. Hudson, in the animal testing or in any of the tests, was there examination

of the CSF fluid?

DR. HUDSON: I don't believe there was. Pat, do you k now?

DR. JENSEN: I didn't see it, and since the material was applied to the CSF, was that a consideration for the FDA in asking for CSF examination?

DR. HUDSON: We didn't ask them to do that. It's a good comment.

CHAIRPERSON BECKER: Dr. Egnor.

DR. EGNOR: This is for Dr. Schlosser.

Regarding the FDA's recommendations about control groups for this, why is it undesirable to compare the efficacy of DuraSeal to the standard way of managing these problems, even if the standard way involves using agents that haven't been approved by the FDA?

DR. SCHLOSSER: It really has to do with how we would interpret the study results at the end, and so I think that while as a neurosurgeon you may say that I'm comfortable with the standard way of managing these patients and if you tell me that this

product is as good as the standard way, that's okay.

On the FDA side, we have to say that for all we know, all of those products are unsafe and ineffective, and in fact, maybe causing increased infections, causing increased CSF leaks because they haven't been studied.

And so to say that this product is equivalent to the heterogeneous standard of care might be to say that it's equally bad, which leaves you with the concept that maybe then you have to show superiority, but then that's a very challenging study to design. How much better do you need to be?

That's also making the assumption that those products don't work when, in fact, they may work but just haven't been studies, and then you're setting them up for a study that they can't complete because they have to show they're better at something that in actuality is equivalent.

And so it's just a challenging design. As Dr. Witten mentioned, it's not that we would not allow them to do such a study if they wanted to, but we simply advised them that we felt there was a weakness

in that design and in our ability to interpret the results of that design.

CHAIRPERSON BECKER: Just to play devil's advocate, I can name you several studies that are currently being done with standard of care therapy that's not proved for stroke prevention, for instance, that are looking at neurological devices against unproved standard of care.

So I don't think it's completely out of the real of question to proceed in that way.

DR. SCHLOSSER: But, okay, to follow up with the devil's advocate though, I would say that studies that are currently underway fall under my first comment, which is that we would allow them to do it. I would be curious if you would tell me studies that have been approved based on the comparison to a standard of care.

Because as we said, we'd be happy to let them do it. Our concern was that it was not a study that would eventually lead to an approval, or it may have problems in leading to an approval.

CHAIRPERSON BECKER: Dr. Haines.

DR. HAINES: But to follow up on that and on your final comments, how does not having that control help us reach a conclusion?

DR. SCHLOSSER: I think that our comment would be that not having the control certainly isn't better than having the control and reaching a conclusion, but our feeling was the opposite, that having the control would not put you in any better situation than you're in right now, that you would have the same problem you have right now if you had that control, and that you may feel as though this number is as good as the control group, but we would feel the whole time that we don't know what that control group means, and that may be you may be relying on a number from a control group that seems okay when, in reality, that's not okay. It's actually a safety problem.

CHAIRPERSON BECKER: Dr. Loftus.

DR. LOFTUS: Unless, just as an argument, you know, as a somewhat pedagogical point, but unless you accepted a control group and developed use of no agent, which was an off-label agent, and an argument

has been made that this is an unacceptable surgical standard. Many of us would disagree with that.

DR. SCHLOSSER: And that was something that was also thought about and, you know, the reasoning behind not taking that approach was simply that the neurosurgeons that were consulted, you know, by the sponsor felt as though that was not an acceptable standard of care to leave those patients open.

And I think that I would agree that the community is probably divided on that issue. I think you could probably find surgeons who, like Dr. Cosgrove mentioned, like the French, who think that closing the dura is just something you do and you probably don't even need to do it, and you could find surgeons who would tell you that you absolutely must have a watertight closure.

And so I think that that's a tough decision to make, given that there probably is an accepted standard of care, but the surgeons that the sponsor was working with, you know, they fell in the second category where they felt it was inappropriate

to leave patients, especially with spontaneous leaks, you know, without any adjunct to dural closure.

CHAIRPERSON BECKER: Dr. Jayam-Trouth.

DR. JAYAM-TROUTH: In the Young study, you know, the dimension of the 846 clean craniotomies, you used that for infection. Was there any indication in that study, you know, as to what the CSF leak rate was, you know, what type of surgery it was and, you know, whether they used anything at all to stop those leaks?

DR. SCHLOSSER: Yeah, they did not mention specifically the CSF leak rate in that study. So we don't have CSF numbers from the Young study.

In addition, of the 846 cases, only 250 were craniotomies, and so all of the leaks from the spine, I would say, are a completely different physiologic problem and aren't really comparable, and then they didn't report what the leak rate was for the craniotomies in that study.

CHAIRPERSON BECKER: Dr. Germano.

DR. GERMANO: For Dr. Schlosser.

In this study, 111 patients that met the

inclusion criteria leaked after experienced neurosurgeons closed the dura. Did you find in your review of the literature that this is the case? In other words, dural closure cannot be accomplished at all?

This is question number one. And question number two: if that is the case for those neurosurgeons that participated in this study, why didn't they select 50 percent of those patients to be enrolled and for the other 50 percent not to be enrolled?

DR. SCHLOSSER: Okay. The first question, I would say that the literature does not report on using Valsalva maneuver to test for a CSF leak. It is something that's done. I wouldn't say it's routinely done, but it is something that's done particularly in the spine, but also in craniotomies to test your dural closure, but it's certainly not something that's done in the 100 percent of cases, and it's not at all reported on in the literature.

In fact, the status of the dural closure prior to closing the galea was not really reported in

almost any of the studies also, and so they never really comment as to whether or not there was CSF leaking through the suture holes or the incision in any of those cases that went on to develop leaks.

So that's information that we kind of have in this study that probably hasn't been really looked at rigorously in these other studies in the literature.

As far as, you know, the result, the fact that everyone leaked, I think I would like to get the sponsor's input, but I think that that would surprise me, that I would have not thought that to be the case. I would have thought that at least a portion of the sutured dural closures would have stood up to that Valsalva.

That wasn't the case. It turns out that all of those patients leaked. Now, you know, why not just exclude all those patients? Well, there's one very pragmatic answer, which is that the study design that was already approved included all of those patients, and so you really would have had to start over with a new study at that point, which you would

have had to have done, of course, only after you completed the study because after the first 40 patients you may have thought, well, we're going to encounter 40 more that won't leak.

And so really at the end you would have had to decide that now after doing the whole study we need to start over.

Now, in hindsight, you know, what would the results of the study have been if we only include spontaneous leakers? Well, we don't know the answer to that question.

CHAIRPERSON BECKER: Dr. Ellenberg.

DR. ELLENBERG: Dr. Schlosser, let me follow up again on the issue of the control group. Given that the sponsor came in with an expectation of hitting above 80 percent success rate, where "success" was defined sa no leakage, it's not clear to me how that argument plays out.

If you were starting in an open field discussion of, well, we really had no concept of how this thing was or was not going to work, I'm sympathetic to that argument and probably to the

approach.

But when we're talking about something based on the pilot studies' literature review is expected to work quite well and it's just a question of how quite well, and you're in the range of 80 percent and you're actually shooting to go as they did to well over 98 percent or 98.2 percent; I'm not sure how that argument works.

Because if the standard of care group was -- I'm sorry. If both groups were equally bad at the 85 percent level or at the 98.2 percent level, I think we would have had a lot of information to deal with.

So if you're talking about no knowledge and you're worried that comparing the control group to the sealant group and they were competing for a place in the eight percent level, so to speak, I'm sympathetic to your argument. But when the expectation is 80 percent, I really don't understand how that argument still holds.

DR. SCHLOSSER: Okay. I think I understand what you're asking. I think there's two questions there, and that is that, you know, why is it

80 percent, and then, you know, why is it that we don't need to test that product against something else rather than just against the number 80. Is that the correct --

DR. ELLENBERG: No, it's the issue of the current control group versus testing against what's in the literature, and in this case it turns out we're basically testing the safety against what's in the literature more than the efficacy.

DR. SCHLOSSER: Right, because I think the efficacy -- I'm not sure that this study design is any worse or any better than having a control group. However, I think that given what we now know about the results of the study, I think that, you know, especially if their control group was, you know, no treatment, you would have had zero percent versus 98 percent as your two groups because, I mean, no treatment, clearly all of those patients would have leaked.

And then if you allowed them to use standard of care and put another number, you know, other devices in, they would have had some other rate

possibly as high as 98 percent or somewhere in between.

And so I think that comparison would have told you the same thing that our efficacy endpoint told you in that we kind of know that the goal of this tool is to prevent CSF from leaking out through the incision in the OR, and they achieved a 98 percent success rate at that.

And so I think that the question regarding the control group is really, as you mentioned, really more one of safety.

DR. ELLENBERG: Absolutely.

DR. SCHLOSSER: But I think that, you know, the safety of that control group is from our standpoint completely unknown. And so I think that you could speculate during the study design that if the numbers came out a little low but similar that maybe you would have some confidence, you know, that the control group was also safe and that the treatment group was safe, but I think that in the end you would have not had anymore assurance.

You know, you're comparing to an unknown.

I mean, you have to make assumptions about that unknown that we're not willing to make because we make people do studies to prove safety. We don't make assumptions about safety.

And so I think in order to evaluate that result you have to make an assumption that we don't routinely make at FDA, and that is that something that hasn't been tested under an IDE study can be assumed to have a certain outcome.

DR. ELLENBERG: But you're asking us to advise you in what seems to me to be a less opportune situation where we're looking at a nonconcurring control group cold from the literature. That's not good in terms of assessment of the safety.

If the control group had a lower profile for safety -- excuse me -- a lower infection rate than the DuraSeal group and the DuraSeal group was as effective as it is now and presumably it would be more effective than the standard of care because there must have been that motivation in bringing this this far along, my sense is that we would have a much better feel for what the safety issues were.

If you didn't know -- not you personally -- if the world doesn't know the safety profile for standard of care, then after this study they would have a better handle on what the safety profile standard of care was in spite of the fact that the control group would by the nature that the standard of care is described, where basically the surgeon is there, there's a problem, there's a leak, and there's a shelf full of options, and the surgeon individually determines based on the type of surgery, the patient condition, et cetera. That couldn't be changed. I understand that, but that is an approach. It's a defined approach. It's what happens every day in the surgery theaters in the United States and apparently not in France --

(Laughter.)

DR. ELLENBERG: -- but it's fairly standard of care.

I simply don't understand why that comparison would have been helpful on the safety side and why it wouldn't be better than what we're being asked to judge.

DR. SCHLOSSER: Well, again, I think there's an assumption being made there, and that is that in the end of the study, the numbers would have come out in a certain way, meaning that the rate would have been higher or would have been lower.

I think that, you know, the opposite could have been true, and I think that the panel could have been given a false sense of security if the numbers had come out the same or if the control group had come out with a higher number. You might have been given the false sense of security that, oh, this device is safe because its number is the same or lower than the control group, whereas in reality all that may have been telling you is that the device is just as unsafe as standard of care.

And I think that the panel may have been, you know --

DR. ELLENBERG: But what's wrong with that answer for this particular application?

DR. SCHLOSSER: Because we don't approve devices based on the fact that they're as unsafe as other unapproved devices. We approve them based on

the fact that they demonstrate a reasonable assurance of safety and effectiveness.

And so I think that the short answer to the question is that we didn't know that the panel would be in a better situation with that study than they're in now, and from a least burdensome approach, this was the least burdensome of the two studies, which in our estimation would give the same level of results and kind of put you in the same position that you would be in with that other study design.

But I will reiterate what Dr. Witten mentioned, which is that that design was an option and that it was not that the FDA would have disapproved the IDE if they had chosen to use a heterogeneous control.

DR. ELLENBERG: I understand that.

DR. SCHLOSSER: We simply advised them we thought there was weaknesses in the design.

CHAIRPERSON BECKER: I think we'll let Dr. Schlosser off the hot seat for the moment and break for lunch. We'll reconvene at one o'clock, and there will be a chance for more questions for the FDA and

the sponsor as well.

(Whereupon, at 12:11 p.m., the meeting was recessed for lunch, to reconvene at 1:07 p.m., the same day.)

AFTERNOON SESSION

(1:07 p.m.)

CHAIRPERSON BECKER: It's now five minutes after one o'clock, and we will resume the panel discussion.

Two lead panel reviewers, Dr. MacLaughlin and Dr. Canady, will open this part of the meeting with the remarks to help focus the deliberations. The panel will then discuss and deliberate on the information in the submission and the information that the sponsor and the FDA presented.

The panel can ask the sponsor or FDA questions at any time. After a general discussion, the panel will address the FDA question. Then there will be a second open public hearing and FDA and sponsor summations. Then the panel will conclude the deliberations and vote on the recommendations concerning the PMA.

The first lead panel reviewer is Dr. MacLaughlin.

DR. MacLAUGHLIN: Thank you very much for setting up this overhead for me because my CD burner

crashed and I don't get a chance to make a fancy presentation, but this brings me back to my old days, anyway, in school.

So what I did was to try to summarize what was done by the sponsor to sort of analyze all of the materials that go into this DuraSeal product, how it was tested, how it's made, and what sort of controls are built in for the ultimate safety of the patient.

And as we've all heard, this device is made to, you know, make sure that we close wounds in the dura that are up to two millimeters in width, and I think what's important to note, too, is that this hydrogel product is an absorbable, cross-linkage polymer of 20,000 molecular weight, and this cross-linking is done in a non-exothermic or endothermic way. It's an isothermic reaction. It happens immediately. So it doesn't generate any local heat, which can sometimes happen in chemical catalysis.

And I think that's a useful thing to point out because I feel that that's another measure of safety. It polymerizes right away, and it doesn't create any local heat, and it's pretty stable, as

you've heard, to 37 degrees C.

And the desired performance characteristics I mention again because they're part of the testing procedure that went on at Confluent Surgical in order to evaluate how well the product that they were getting is performing.

So it needs to be easy to use and needs to be absorbable, and it had to adhere to the dura and not to other structures, the sort of lubricous characteristic that we've heard about already, and it needs to be biocompatible. And I think many of these things were tested in these products over time, and I think it's important to note also that everything you use in this product is bought off the shelf. I mean certain items are made to Confluent's specifications, but they're all available and used widely in lots of other applications, and that was important to me in this analysis, and there are three or four different vendors of the materials. I didn't mention all of the vendors for the plastic stuff, for the syringes and the caps and the containers and all of that because they have all been covered, I think, by the FDA under

many other applications.

But all of the material that the company gets is delivered to the site, and they sort of package it together after testing it. It goes to another company to ship it out. So there are controls built in that I'll talk about in a minute for that.

So, anyway, I think a couple of points that I wanted to raise in this analysis was what Confluent does once they get the product and why they've arrived at certain specifications for the product in particular, some questions I really want to raise in that.

The other thing that is important is that the breakdown products of this polymer that you heard about in this morning's discussion are basically the same as the product itself. So you don't need to worry about a new, you know, actor in the game for toxicity. You're really looking at the same thing, going, dissolution, being cleared at the end of the day. So that's important to me.

So how happy am I with all of this? You know, I sort of looked at it to say what would I

really want to have done and have accomplished, and the performance characteristic testing at the site -- this is not in the patient. It's either in the animal or in vitro -- has to meet certain standards that the company sets, and this is a few questions I wanted to raise here as to why they're set.

The reconstitution of the PEG, this polymer in its buffer, you know, should happen in give minutes. It's simple. You're just going to dissolve the material. It has to be completely in solution quickly. That's easy to analyze, easily understood.

The gel time is three and a half second. They tested this by taking the product and just squirting it from one of those syringes into a beaker that has a stir bar in it. Boom, in three seconds it has solidified. Simple test, not hard to confuse. That's important because it relates to the, you know, chemical composition of the products as they're mixed.

One thing I did have an issue with though is this so-called swelling characteristic. This is 200 percent, and that's I understand why it's not good to have a lot of swelling in the brain. I don't

understand why 200 percent is the standard they picked -- excuse me -- the specification they picked because when they analyzed the material, their own data shows it to be way lower than that. So why pick a huge window when it really should be maybe smaller. I'd like some feedback on that

The hydrolysis in vitro is one and a half to four days at 60 degrees Centigrade, which is called an accelerated test. So you know the material is going to be put together. You know it's going to go into a patient. You know it's going to dissolve and be reabsorbed. So one of the chemical characteristics you can test periodically is to make your polymer, put it in a solution, heat it up, and decide how long it takes to fall apart.

So they have this accelerated test and then they have the 25 degrees C. test, and I don't understand why we have those two tests, why they're necessary. I think the 25 degree test makes sense to me. The 37 degree test I have to say doesn't make sense to me because I don't understand what it's telling us. It's not what's going on with the

patient. The patient is on 140 degrees, you know. They're 25 degrees.

So, you know, I want some feedback on why that's a standard that they picked. What is that telling you about the safety of that product to have that measure? Real time makes more sense. Real temperature makes more sense to me.

So the application, this is the syringe integrity polymer, tips and all of that. They went through a series of trials actually using different kinds of products, spraying them, testing for the pattern of spray, how well things polymerized in place, and arrived at, I think, a reasonable set of materials, a reasonable set of syringes, a reasonable set of tips, applicator tips. All of that seems to make good sense to me. I don't have any concerns about that.

The other thing that's careful to inspect every time new products are shipped -- remember this is coming from vendors into your facility -- you have be sure that their oxygen content, especially of the sealed glass vial, is important and the buffer pHes of

the mixing reagents are proper. That's something they test all the time. I think they should test all the time because it does affect how much polymerization one gets and how stable the product is.

So just doing a squirt test and seeing polymerization doesn't tell you how long it's going to last. It has to be many different levels of testing, which I think, in fact, they do.

The absorption and the sealing tests Dr. Hudson spoke about, I think they're very straightforward. I didn't have any trouble understanding the goals, understanding the data, or coming to the conclusion that I didn't think there was any toxicity, especially when you consider the historical controls which were done on a lot of these materials. Lots of studies have been done on these materials in the literature, and you look at how much of this material is available in one or two applications into a head. You've got so little of this product around. I don't see toxicity being a major player here of any of the components.

What I'm more concerned about is why

certain specification standards were set and how they're tested for.

So another issue is this package integrity, which you have to consider. They're putting lots of different components into a plastic container. It's going to be stored for so many months. It's going to be shipped out to place. How hot can it be? How cold can it be? Is it going to keep bacteria out? Are you going to introduce, you know, bad things through the package itself? I think that's pretty well controlled for, too.

I don't have any difficulty either understanding their goals, the analysis that they used, or the results that they have. I think it's fairly clear. No problems there.

The shelf life issues, though, is another one of these accelerated versus nonaccelerated types of test. When they sterilize the material, it gets irradiated, and if you measure where the irradiation falls and measure how much radiation occurs from the surface through the material, you can get minima and maxima of radiation.

So you're like to be sure everything is stable. So you do a series of experiments in which everything gets the maximum dose versus the standard irradiation of the material.

That is underway, and as far as I know, those results on performance testing have not been completed, but are pending, and I'd like to know if they are completed now because you can have effects on the ultimate product based on irradiation, not of the patient, but of the material as it's sterilized.

So that's another thing I was interested in hearing some more about, and that has to do with acceleration, too. That's a shorter feedback loop to find out if your product is clear or not.

So the toxicity studies and the biocompatibility studies, I think, are also very straightforward to me. All of the non-hydrogen products have historical controls which I have no quibble with, and everything else was tested, I think, pretty much by very standard and well accepted criteria for, you know, genotoxicity, all of the things that have been mentioned actually by the FDA

presentation.

Carcinogenicity, as I say, was not tested because of historical controls, which I think are reasonable, and I think the in vivo testing for biocompatibility relating to the seal test in the dogs and the imaging studies, all of the other in vivo animal studies I thought were reasonable because I think they did approximate what happens in the patient. I think it approximated how much material you put in, where you're putting it in, how long they're going to be in there.

So it sort of matched the four to eight week study period, not the three-month control stuff, but the four to eight-week stuff. I thought it matched pretty well what was going on in the patient and no untoward or no adverse effects were not, and I think that's pretty reasonably done.

The extraction was a slight variation on the theme where the hydrogel was extracted and ejected into these spaces referred to by the FDA, and there was no adverse effect there either.

So when we talk about, you know, the dye

or specific components having effects, I think of the worst case scenario is right next to the implant or right next to the injection. That's where the dose is highest. That's where if you're going to have a bad effect you're going to see it there, and none was seen.

So I'm kind of back and forth in my own mind about whether that's a useful study to do in a different way.

The last point I think I want to reach is the fetal toxicity study and the proliferation inhibition study. The fetal toxicity study and the maternal fetal compartment study was begun at four days of pregnancy. So a small caveat is while it may be difficult to establish when a rat is pregnant, you know, a lot has happened in four days.

So you start injecting at four days. You know things are pregnant, and you know the animals are pregnant. So from that day on you know there's no untoward effect.

It's just a caveat. I'm not saying do anything sooner. It's just a limitation. It doesn't

cover, you know, the nidation period or getting pregnant or anything like that, but again, I don't have any suspicions of any of this material causing any problems, but it's a caveat that you've already had fertilization. You've already had nidation. You're now starting to develop. In a 21-day pregnancy, you're already four days in. So that's a small point.

The proliferation and inhibition studies on the cell growth where they took extracts of the material, put it into cell culture with four or five cell lines I thought was completely uninformative actually. I didn't know exactly what they were going for. I understand you want to see if it inhibits our, you know, causes proliferation of cell growth, but to me proliferation is changing rate of growth. Awful hard to do in four days. Okay?

If you put something into culture, there's no discussion of what the doubling times of the cells were. You know that it was an empty T assay, but you don't know what its states of competency were. We don't have any other data around that, and I'm not

sure what it was designed to tell us.

You know from the histology data that there isn't a lot of proliferation at the site of these things. You don't see inhibition of cell growth. You don't see inhibition of cell growth. You don't see wound failure. You don't see the things that would be characteristic of stimulation or inhibition of cell growth. So I don't know what that was done for, and maybe I could be informed about that.

So overall, I think I agree pretty much with the FDA's determination that this material does not contain anything that I think is risky. I don't think by themselves those components contribute to any of the side effects we've been talking about in sealing the dura. I don't see any smoking gun there, and I think they've been reasonably tested.

My concerns are what happens at the factory evaluating all of the things that come in from different sources and what their standard of performance is going to be every time you get a new lot, every time you ship things out.

How long are things stable? Six months it says on the label now. That's the only thing you have real time data for. Any extension of that needs more data, that sort of thing.

I'm staying right within the confines of physiology and your own data.

So that's really all I have to say.

CHAIRPERSON BECKER: Thank you.

Does anybody on the panel have any questions for Dr. MacLaughlin?

(No response.)

CHAIRPERSON BECKER: Would anybody at Confluent Surgical like to address some of the questions raised by Dr. MacLaughlin at this point or in the summation later? Your choice.

DR. CAMPBELL: Thank you, Dr. MacLaughlin. Those are some excellent observations. We'd like to address that.

I'd like to introduce Amar Sawhney. He's the president and CEO of Confluent Surgical, founder of the technology.

I tried to keep a list of your questions

one by one. So I'll try to address them. If I miss anything, I trust you'll let me know.

DR. MacLAUGHLIN: I sure will.

DR. CAMPBELL: The first comment you had concerning the swelling and the 200 percent swelling specification, you're correct. That is a specification that we test for. Every lot that is released we evaluate the amount that the hydrogel expands.

The way the test is performed is we weigh it initially, a sample. Then we put it in PBS for 24 hours, weigh it after 24 hours, and the percent increase in weight is the 200 percent specification.

DR. MacLAUGHLIN: I know how you do it. I'm just wondering why you picked 200 percent.

DR. CAMPBELL: The 200 percent specification was like several ways. One, we've looked at competitive products that are currently used in neurosurgery of those gelfoam, flow seal, surgicel, others. Those products can swell in a similar test that much or more, 50 to 200 percent or more.

We've also performed as you're aware

studies in canine and rat models. The canine model arguably is a worse case model where you have a durotomy which has been performed in an animal with a fairly small cranial vault compared to humans. You've applied an appreciable amount of DuraSeal there, similar thicknesses to what you would have in humans. You have not removed any kind of brain parenchyma or tissue underneath. So any swelling is felt by the brain. There's no space or void to fill, and the bone flap is replaced and the tissues are sutured over the top.

So arguably, that's a worst case scenario. we perform two different preclinical studies in canines using that model, and in both studies we found no mass effect, no residual effect from that.

DR. MacLAUGHLIN: If I could say, I have to agree with that. I agree with your data. What I'm saying is you're allowing, you know, 100 percent more space to be in this product than you have. I'm just saying make it the standard that you have because if you allow more space, you don't have that data in the dog. You have the data that you have, which is maybe

110 or whatever it is. I forget the specific number, how much percent you actually get of swelling.

DR. CAMPBELL: Well, a lot of those testings were performed with formulations where we were getting up to 200 percent swelling.

DR. MacLAUGHLIN: But none seen. I didn't see any in your data.

DR. CAMPBELL: We have, as you mentioned, refined manufacturing processes, and typically our swelling is less than that right now.

DR. MacLAUGHLIN: Sure.

DR. CAMPBELL: However, we have data that shows that it's safe at 200 percent, and to maintain manufacturability so that lot to lot variations don't affect this, we feel that 200 percent is an acceptable, safe level to select.

DR. MacLAUGHLIN: Well, I have to say I haven't seen the 200 percent data. You know, it was like looking at your volatiles, how much organic volatiles. I didn't mention that in the presentation, but there's a specification that say how much organic volatiles you can have, which are toxic if you get

them in high enough concentrations.

I'm not saying we're there yet. We're definitely not there, but the window is really big compared to what you actually have in your lot after lot testing. So I'm just trying to make some determination as to why you need these big windows when your product isn't that big.

DR. SAWHNEY: Amar Sawhney. I'm the president and CEO of Confluent.

Let me attempt to respond. The window is actually sort of not that big because volumetric swelling takes place with the cube function. So while thickness doesn't expand that much --

DR. MacLAUGHLIN: Yes.

DR. SAWHNEY: -- the weight gain can be substantial. So it doesn't take much to reach that, the 200 percent, and when we had done the studies, the data that we have reported on the lot to lot variation is for the more recent lots.

The testing that was done on the canine study with the original materials did have that amount of swelling. So while it is not explicitly pointed

out for that particular lot, those were studied. Then we have backed down and proved our manufacturing techniques, but we have tested the worst case scenario in those animal studies.

Also, the animal studies are predisposed because of the limitations, the limited space and the fact that no parenchyma is removed. We believe we have tested the worst case scenario both from a formulation and an animal study perspective.

DR. MacLAUGHLIN: Right. I think it's important for us to see the data. We've only seen your latest stuff, not the earlier stuff. I think that's an important consideration in deciding what the specifications of this material would be.

DR. SAWHNEY: Okay. Good point.

DR. CAMPBELL: A second point you mentioned was our disappearance testing, our in vitro disappearance testing. We initially started off by doing a test which is similar to the swelling test that I described where we get a piece of gel, put it into 37 degree PBS, and then observe it on a daily basis and determine the time at which the gel has

completely gone into solution and there's no solids remaining.

If you do that in PBS doing that test, it's up to 40 days or so at which that test occurred or takes for the material to dissolve.

In order to streamline and since this is a test which is used for lot release, in other words, every lot that we manufacture needs to pass this test, we formed in-house testing where we determined the correlation of disappearance rate with temperature.

In other words, as you know, as you increase the temperature, the hydrolysis rate will increase also, and we did it with multiple lots using multiple lots of polymer. We determined the correlation of temperature and degradation rate and correlated that and determined a way to do the test, the same test, where you're determining -- you're demonstrating disappearance, but you do it at a much higher temperature, and it allows you to do it in less than a week.

DR. CAMPBELL: Right.

DR. SAWHNEY: Let me amplify on that a

little bit. It's a standard chemical reaction. It's a first order kinetic that's taking place. It's an erraneous (phonetic) plot that you do. Very similar work is done if you look at pharmaceuticals. Their stabilities and standard kinetics can be accelerated.

It's also a bulk hydrolysis. So it is not relative to say sutures which may not have a penetration of the water. Here the material is entirely permeable because it is substantially water. So the bulk hydrolysis can be adequately accelerated with first order kinetics using an elevated temperature and provides a robust extrapolation and allows you to conduct a study and a test as a release criterion and an appropriate time, and we have data demonstrating that correlation.

DR. MacLAUGHLIN: But I guess my point about this is the same as the previous point. You have data in the patient or in the animals. You know how long it takes to go away at that temperature. I agree with you it's first order kinetics, but three or four major elements play: pH, oxygen concentration to get your ultimate right cross-linking.

And what you're doing is correlating one temperature with another, and that higher temperature has no correlate in the animal. So you don't know that that's telling you about the structural integrity of this material. You know that is' faster degrading than at 25 degrees, and I like the conformity of the sort of real time/real temperature data analysis of this material because it goes together really fast. Your own data show oxygen concentrations are very important, and I'm just saying I want a little more justification then.

You can release it faster because there isn't a correlation going back to the patient.

DR. SAWHNEY: Actually let's talk about oxygen. Oxygen concentration during the cross-linking is, frankly, not important. Oxygen is important as part of the manufacturing process wherein oxygen radicals in the presence of radiation sterilization can end up with G incision (phonetic) after molecules, and that's why the keep the oxygen concentration.

Once the solution is reconstituted, the presence or absence of oxygen, it really doesn't have

any material effect to it.

DR. MacLAUGHLIN: I'll concede that point. What I'm saying is that when you look at your own analysis of what a product is, all I'm saying is that I guess I don't understand why faster is better. I mean, what advantage does that bring to the table?

DR. CAMPBELL: The main purpose for this disappearance test was just to demonstrate that the material went into complete solution after a certain amount of time.

DR. MacLAUGHLIN: Yes, I understand that. I'm talking about the elevated temperature analysis.

DR. CAMPBELL: Exactly. And the elevated temperature just allows us to demonstrate that in a week rather than 40 or 50 days.

DR. SAWHNEY: It's just a release study. It's a test, and once we have studied the material and we understand its behavior in vivo, now it's more a test of showing that one lot is similar to another lot, and that allows us to do the testing.

DR. MacLAUGHLIN: I understand. We can agree to disagree on this, I guess.